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PHILIP S. JOHNSON
JOHNSON & JOHNSON
ONE JOHNSON & JOHNSON PLAZA
NEW BRUNSWICK, NJ 08933-7003

EXAMINER	
SHAFER, SHULAMITH H	
ART UNIT	**PAPER NUMBER**
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/833,222	QIN ET AL.	
	Examiner	Art Unit	
	Shulamith H. Shafer, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 June 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *9-12 and 14-22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8 and 13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *4/11/2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *9/13/2001*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Status of Application, Amendments, And/Or Claims

The Examiner and Art Unit prosecuting your application in the USPTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Shulamith H. Shafer, Art Unit 1647.

Applicant's election with traverse of Group I, claims 1-8 and 13, drawn to nucleic acid molecules of SEQ ID NO:9 encoding amino acids 1-1090 of SEQ ID NO:10 and variants thereof in the reply filed on 1 March 2004 in response to the 26 June September 2003 office action is acknowledged. The amendment to Claim 4 has been noted and entered into the record. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-8 and 13 are under examination. Claims 9-12, 14-22 have been withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Objections

Specification:

The instant application is not fully in compliance with the sequence rules, 37 CFR 1.821-1.825. Specifically, sequences are disclosed on page 62, lines 8, 9, 13, 14 and 23, page 63, line 23 bridging 64, lines 1 and 2 and pages 66-69 without the required reference to the relevant sequence identifier. Appropriate correction is required.

Information Disclosure:

The information disclosure statement filed 13 September 2001 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because references 17 on page 2 of 3, and 32 on page 3 of 3 are in improper format. They have been lined through because reference 17 does not include the year and volume and reference 32 does not include the volume. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609.05(a).

Claim Rejections

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, and 13 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 11, 12 and 18 of Application 10/119624. The Examiner has issued a Notice of Allowance of these claims, but this application is not yet an issued patent. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented; the rejection will become non-provisional when the application issues as a patent.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, for example, *In re Berg*, 140 F.3d 1428 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (Fed. Cir. 1985).

Although the conflicting claims are not identical, they are not patentably distinct from each other for the following reasons.

The claims in the reference application (10/119624) disclose an isolated nucleic acid molecule encoding a polypeptide comprising SEQ ID NO:10 (Claim 1a), a polynucleotide comprising SEQ ID NO:9 (1b) and a polynucleotide comprising a sequence that is complementary to the polynucleotide of SEQ ID NO:9 or SEQ ID NO:10. Since these sequences are the referenced sequences for the variants encompassed by the instant Claims 1 and 4, the copending claim renders Claims 1 and 4 of the instant invention obvious because a species renders obvious its genus. Claims 2 and 3 of the reference application recite the polynucleotide being RNA (2) and the polynucleotide being DNA (3), Rendering obvious claims 2 and 3 of the instant invention. Claims 11, 12 and 18 recite an expression vector, a recombinant cell comprising the expression vector and a method for expression a $\alpha_2\delta$-4 calcium channel subunit protein in a recombinant host cell. These claims render Claims 5-8 and 13,

which recite an expression vector (Claims 5 and 6), a recombinant host cell (Claims 7 and 8) and a method for expression a α2δ-4 calcium channel subunit protein in a recombinant host cell (Claim 13) of the instant invention obvious. Thus, Claims 1-8 and 13, are all rendered obvious by the cited claims in the reference application.

35 U.S.C. §§ 101 and 112, First Paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim(s) 1-8, and 13 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible, substantial or specific asserted utility or a well established utility.

When determining whether an applicant has described the utility of invention, one has to determine whether the applicant has described a well-established utility. If not, has the application made any assertion of specific, substantial and credible utility. A credible utility is assessed from the standpoint of whether a person of ordinary skill in the art would accept that the recited or disclosed invention is currently available for use. In contrast to general utility, a specific utility will be specific to the claimed subject matter. A substantial utility defines a real world utility of the invention and utilities that require or constitute carrying out further research to identify or reasonably confirm a real world context use are not substantial utility (see utility guidelines, in Federal Register January 5, 2001, Volume 66, Number 5, Pages 1092-1099).

The claims of the instant invention are drawn to an isolated and purified nucleic acid molecule of SEQ ID NO:9 which encodes a polypeptide comprising SEQ ID NO:10,

molecules complementary to the polynucleotide of SEQ ID NO:9, splice variants, fragments, an expression vector, a recombinant cell and a method for expressing the protein in a recombinant host cells. The protein disclosed in SEQ ID NO:10 is designated in the specification as a $\alpha_2\delta$-4 calcium channel subunit. To analyze the utility of the claimed invention one must determine if the protein of SEQ ID NO:10, encoded by the polynucleotide of SEQ ID NO:9 has a well-established utility or a credible, specific and/or substantial asserted utility.

Applicants disclose that molecules encoding the channel subunit ($\alpha_2\delta$-4) were identified from an expressed sequence tag database (Example 1, page 61) and isolated using a recombinant expression system (page 7, lines 6-8, Example 2, page 62). The molecules were identified as members of the $\alpha_2\delta$ subunit family by virtue of being 40% identical to the mouse calcium channel $\alpha_2\delta$-3 subunit, 36% identical to human calcium channel $\alpha_2\delta$-2a subunit and 34% identical to the human calcium channel $\alpha_2\delta$-1a (page 51, lines 18-23).

Applicants teach that a calcium channel $\alpha_2\delta$ subunit is a component in every voltage-gated calcium channel purified from various mammalian tissues and that this subunit regulates most of the properties of the calcium channels (page 5, lines 6-8 and lines 14-15). The specification asserts that the $\alpha_2\delta$ subunit alters the binding of neurological and cardiovascular drugs to the ion channel pore-forming α_1 subunit and that gapapentin, a novel anticonvulsant drug, binds directly to the calcium channel $\alpha_2\delta$ subunit (page 5, lines 17-21).

Applicants assert that the recombinant DNA molecules of the instant invention are "useful for isolating homologues of the DNA molecules, identifying and isolating genomic equivalents of the DNA molecules and identifying, detecting or isolating mutant forms of the DNA molecules" (page 7, lines 9-14) and that "DNA encoding a calcium channel $\alpha_2\delta$-4 subunit from a particular organism may be used to isolate and purify homologues of calcium channel $\alpha_2\delta$-4 subunits from other organisms" (page 19, lines 13-15). However, this is not a specific utility for recombinant DNA encoding the $\alpha_2\delta$-4 channel subunit protein. Any isolated DNA or RNA molecule may be used to identify, isolate and detect homologues and/or binding partners.

Applicants teach Northern blot analysis using a human $\alpha_2\delta$-4 N-terminal specific probe shows that the transcript for $\alpha_2\delta$-4 subunit is most abundant in human heart and skeletal muscle (Example 6, pages 72-74). The specification teaches that there is differential expression of the $\alpha_2\delta$-4 subunit in human tissues; the protein is expressed most strongly in the pituitary, Paneth cells of the gut, erythroblasts of fetal liver and the cells of the adrenal glands (Example 11, pages 81-83; Table 2, page 82-83). While Applicants assert that the results suggest a role for this specific subunit in specific tissues, the specification does not teach any nexus between this particular subunit and any known physiological or pathophysiological process. In the absence of such a disclosure what is the utility of the claimed invention? The fact that this subunit may form a functional calcium channel when transfected into a host cell containing three additional calcium channel subunits does not provide a real world utility of the instant invention since the specification does not disclose any significance of the channel; rather this is an invitation to further experimentation to additionally characterize and identify a function for this channel subunit. Applicants assert that the recombinant protein of $\alpha_2\delta$-4 subunit is useful (1) in identifying modulators of the $\alpha_2\delta$-4 calcium subunit (page 7, lines 13-14); (2) for identifying compounds that alter $\alpha_2\delta$-4 calcium channel subunit protein activity in a cell (page 9, lines 13-14) or *in vivo* (page 43, lines 21-22); and (3) screening for compounds that modulate the expression of DNA or RNA encoding a calcium channel $\alpha_2\delta$-4 subunit (page 43, lines 18-19). However, these are not substantial, real world utilities for the instant invention. Why would one wish to screen for compounds that modulate the expression or activity of DNA or RNA encoding for the $\alpha_2\delta$-4 subunit, or that modulate the expression or activity of the protein itself in the absence of a <u>substantial</u> utility for this particular subunit? Indeed, Arikkath and Campbell (2003, Current Opinion in Neurobiology, 13:298-307) teach that the effect of $\alpha_2\delta$-4 subunit on biophysical properties of currents and the ability to modulate other α_1 subunits is still undetermined (page 300, column 2, last paragraph). The reference teaches that there are no known spontaneous mutations of this subunit, thus no known phenotype associated with aberrant functioning of this subunit (page 305, Table 2). Qin et al (2002, Molecular Pharm 62:485-496) teach that the "$\alpha_2\delta$-4 subunit has limited

distribution in special cell types of the pituitary, adrenal gland, colon, and fetal liver". However they also state "Whether the $\alpha_2\delta$-4 subunit plays a distinct physiological role in select endocrine tissues remains to be demonstrated" (page 485, abstract).

Applicants assert that a functional $\alpha_2\delta$-4 may bind gabapentin (page 40, line 14). The specification also discloses that a cell expressing recombinant $\alpha_2\delta$-4 subunit would be useful in identifying a compound that inhibits gabapentin binding (page 10, lines 1-10, page 43, lines 1-16). However, this asserted utility is not found to be credible in view of evidence to the contrary. Qin et al. teach that $\alpha_2\delta$-4 lacks the gabapentin binding motifs (page 485, abstract) and that Cos-7 cells overexpressing $\alpha_2\delta$-4 subunits fail to bind gabapentin (page 493, column 2 last paragraph bridging page 494, column 1 and 2, and page 494, Figure 9B).

Therefore, the asserted use of the instant invention is not considered to be supported by either a credible, specific and substantial asserted utility since no credible, specific and substantial function can be ascribed to the protein encoded by the isolated, purified nucleic acid of SEQ ID NO:10.

The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sup. Ct, 1966). The court found that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

Claim(s) 1-8, and 13 also rejected under 35 U.S.C. 112, first paragraph. The specification does not provide a well-established utility, nor a specific and substantial asserted utility. Furthermore, due to the large quantity of experimentation necessary to determine any relationship of $\alpha_2\delta$-4 subunit to a specific physiological or pathophysiological function, such that it can be determined how this subunit functions in

the context of an ion channel complex, and the lack of direction/guidance presented in the specification directed to identifying binding partners for the $\alpha_2\delta$-4 subunit, the absence of working examples directed to same, the complex nature of the invention, the state of the art as to the obscure role of this $\alpha_2\delta$-4 subtype, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention.

Furthermore, in addition to the issues raised in the utility rejection, the claimed invention is not enabled for reasons set forth below. If the utility rejection was to be withdrawn, these rejections would remain.

The specification does not reasonably provide enablement for: (a) a nucleic acid encoding a protein having at least a 95% identity to a polypeptide comprising SEQ ID NO:10; (b) a nucleic acid molecule that is complementary to the polynucleotide of (a); (c) a nucleic acid molecule comprising at least 15 sequential bases of either of the above polynucleotides; (d) nucleic acids that hybridize to either of the above polynucleotides; and (e) nucleic acids that encode splice variants of a human $\alpha_2\delta$-4 subunit of a calcium channel. The specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims.

The claims encompass variant nucleic acids that encode variant polypeptides. These claims are overly broad since insufficient guidance is provided as to which of the myriad of variant nucleic acids encode polypeptides which will retain the characteristics of an $\alpha_2\delta$-4 calcium channel subunit. While the claims are directed to variant nucleic acids encoding polypeptides, Applicants do not disclose any actual or prophetic examples on expected performance parameters of any of the possible encoded variants of an $\alpha_2\delta$-4 calcium channel subunit. It is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. For example, Mickle et al. (2000, Med Clin North Am 84:597-607) teach that cystic fibrosis (CF) is an autosomal recessive disorder caused by abnormal function of a chloride channel, referred to as the cystic fibrosis transmembrane conductance regulator (page 597). Several mutations can cause CF, including the G551D mutation. In this mutation, a glycine replaces the aspartic acid at

position 551, giving rise to the CF phenotype. In the most common CF mutation, delta-F508, a single phenylalanine is deleted at position 508, giving rise to the CF phenotype, thus showing that even the substitution of a single amino acid in the entire 1480 amino acid CFTR protein sequence can have dramatic and unpredictable effects on the function of the protein. Additionally it is known in the art that even a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. For example, Voet et al. (1990, Biochemistry John Wiley and Sons Inc.) teaches that a single Glu to Val substitution in the β subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in a homozygous individual, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia (pages 126-128, section 6-3A and page 230, column 2, first paragraph). Additionally, Yan et al. (2000, Science 290:523-527) teach that in certain cases, a change of only two amino acid residues in a protein results in switching the binding of the protein from one receptor to another. The amino acid sequence of a polypeptide determines its structural and functional properties, and the predictability of which amino acids can be substituted is extremely complex and outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the polynucleotide and the encoded protein are lacking, it is unpredicatable as to which variations, if any meet the limitations of the claims. Applicants are required to enable one of skill in the art to make and use the claimed invention. However, the claims encompass polynucleotides and encoded polypeptides which the specification only teaches one skilled in the art to test for functional variants. It would require undue experimentation for one of skill in the art to make and use the claimed nucleic acids. Since the claims do not enable one of skill in the art to make and use the claimed nucleic acids, but only teaches how to screen for the claimed nucleic acids, and since detailed information regarding the structural and functional requirements of the polypeptides are lacking, it is unpredictable as to which variations, if any, meet the limitations of the claims. Thus, since Applicants have only taught how to test for nucleic

acids encoding polypeptide variants of the $\alpha_2\delta$-4 calcium channel subunit, and have not taught how to make polypeptide variants of a functional $\alpha_2\delta$-4 calcium channel subunit, it would require undue experimentation of one of skill in the art to make and use the claimed invention.

Furthermore, the specification does not reasonably provide enablement for a host cell comprising an expression vector wherein the host cell is not isolated or cultured. Claims 7 and 8 are directed to a broad genus of host cells comprising an expression vector which, in turn, comprises the claimed DNA. The specification contemplates two subgenera in which such host cells can be made and used. Specifically, the specification contemplates making and using the host cells in culture and in gene therapy.

Case law directs that the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim non-enabled. The standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more than is normally required in the art. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984) (prophetic examples do not make the disclosure nonenabling). However, claims reading on significant numbers of inoperative embodiments would render claims non-enabled when the specification does not clearly identify the operative embodiments and undue experimentation is involved in determining those that are operative. *Ibid.*; *In re Cook*, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971). Since the instant specification asserts that the claimed host cells can be made and used in two contexts the instant fact pattern corresponds to the second situation wherein the claims encompass a significant number of inoperative embodiments and thus should be rejected under 35 U.S.C. § 112, first paragraph, as not being enabled for the full scope of the claims.

The specification discloses that nucleotide constructs comprising the claimed gene can be used to genetically engineer host cells to express such products in vivo and that these products can be used in gene therapy approaches (page 52, lines 4-23 bridging page 53, lines 1-10). However, the specification does not teach any methods

or working examples that indicate the claimed nucleic acid is introduced and expressed in a cell for therapeutic purposes. The disclosure in the specification is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. For example, the specification does not teach what type of vector would introduce the claimed nucleic acid into the cell or in what quantity and duration. Relevant literature teaches that since 1990, about 3500 patients have been treated via gene therapy and although some evidence of gene transfer has been seen, it has generally been inadequate for a meaningful clinical response (Phillips, A., J Pharm Pharmacology 53: 1169-1174, 2001; abstract). Additionally, the major challenge to gene therapy is to deliver DNA to the target tissues and to transport it to the cell nucleus to enable the required protein to be expressed (Phillips, A.; pg 1170, paragraph 1). Phillips also states that the problem with gene therapy is two-fold: 1) a system must designed to deliver DNA to a specific target and to prevent degradation within the body, and 2) an expression system must be built into the DNA construct to allow the target cell to express the protein at therapeutic levels for the desired length of time (pg 1170, paragraph 1). Therefore, undue experimentation would be required of the skilled artisan to introduce and express the claimed nucleic acid into the cell of an organism to treat disease. Additionally, gene therapy is unpredictable and complex wherein one skilled in the art may not necessarily be able to introduce and express the claimed nucleic acid in the cell of an organism or be able to produce the encoded protein in that cell.

Due to the large quantity of experimentation necessary to introduce and express the claimed nucleic acid in a cell of an organism for therapy, the lack of direction/guidance presented in the specification regarding how to introduce the claimed nucleic acid in the cell of an organism to be able produce the encoded protein, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of transferring genes into an organism's cells, and the breadth of the claims which fail to recite any cell type limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Please note that this portion of the rejection could be overcome by amending the claims to recite, for example, "An isolated host cell..." because such an amendment would clarify that the claims are directed only to host cells which are to be made and used in culture as described in context 1) above.

Claims 1-3, 5-8 and 13 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim (s) contains subject matter which was not described in the specification in such a way as to reasonably convey to to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The claims are drawn to isolated nucleic acids encoding polypeptides having at least a 95% to a polypeptide comprising amino acids 1 to 1090 of SEQ ID NO:10, and variants and fragments thereof. The claims do not require that the polypeptide possess any particular biological activity, nor any particular conserved structure, or other disclosed distinguishing feature. Thus, the claims are drawn to a genus of nucleic acids that is defined only by sequence identity or hybridization ability.

To provide evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product or any combination thereof. In this case, the only factor present in the claim is a partial structure in the form of a recitation of percent identity. There is not even identification of any particular portion of the structure that must be conserved. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide written description of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the

'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more that a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See Fiddes v. Baird, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO:10, but not the full breadth of the claims meet the written description provision of 35 U.S.C. 112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. 112 is severable from its enablement provision (see page 115).

35 U.S.C. § 112, Second Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-3, and 13 are rejected under 35 U.S.C., second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1(d) recites "hybridizes under stringent conditions". These could be low or high stringency conditions. The specification discloses that there are large numbers of hybridization techniques known in the art (page 30, lines 19-21), and cites one by way of example (page 31, lines 2-16) but does not disclose a specific one to be used in the instant invention. Since neither the specification nor the prior art provides an unambiguous definition for "stringent conditions", the metes and bounds of the claim cannot be determined. Claims 1 (e), (f) and (g) recite "a splice variant of a human $\alpha_2\delta$-4 calcium channel". The $\alpha_2\delta$-4 molecule is a calcium channel subunit protein, and does not encompass a complete calcium channel, which is made up of at least four subunits.

Claims 2 and 3 recite "the nucleic acid molecule of claim 1". Claim 1 consists of groups a-g, each of which recites a nucleic acid molecule. It is unclear which of the nucleic acid molecules identified in Claim 1 are recited in Claims 2 and 3.

Claim 13(a) recites "transferring" an expression vector. It is unclear how one transfers an expression vector into a cell.

35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1, 3, 5-8 and 13 are rejected under 35 U.S.C. 102 (a) as being anticipated by Brown and Bertelli (22 March 2001, WO 01/19870 A2). Brown and Bertelli teach a nucleic acid molecule encoding a polypeptide that is 97.5% identical to polypeptide of SEQ ID NO:10 (Sequence 52) in the patent, see also enclosed sequence comparison), thus claim 1 is anticipated. The WO reference also teaches DNA encoding the protein, thus anticipating claim 3. Brown and Bertelli disclose recombinant vectors comprising the disclosed nucleic acid (page 15, line 30, page 50, claim 40) thus anticipating claims 5 and 6. They also teach recombinant host cells (page 18, lines 19-34, page 50, claim 44) thus anticipating the limitations of claims 7 and 8. The reference also teaches the

production of recombinant polypeptides and isolation of such polypeptides from a cell culture system (page 19, lines 1-16), thus anticipating the limitations of claim 13. Therefore, Thus, the teachings of Brown and Bertelli anticipate all the limitations of Claims 1, 3, 5-8 and 13.

35 U.S.C. § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claim 2 is rejected under 35 U.S.C. 103(a) as being unpatentable over Brown and Bertelli (22 March 2001, WO 01/19870 A2) in view of Klugbauer et al. (1999, Journal of Neuroscience 19:684-691). The teachings of Brown and Bertelli are outlined in detail above. Brown and Bertelli teach a nucleic acid molecule encoding a polypeptide that is 97.5% identical to polypeptide of SEQ ID NO:10. Brown and Bertelli do not teach the nucleic acid wherein the polynucleotide is RNA. Klugbauer et al. teach the cloning an expression of two novel calcium channel subunits, an $\alpha_2\delta$-2 and an $\alpha_2\delta$-3

(page 684, abstract, page 685, figure 1) subunit. The reference teaches the isolation of RNA and Northern blot analysis identifying mRNA for each of the subunits (page 684, column 2, last paragraph and page 686, figure 2). It would have been obvious to the person of ordinary skill in the art at the time the invention was made to identify and isolate RNA (using the teachings of Klugbauer et al) encoding a polypeptide that is 97.5% identical to polypeptide of SEQ ID NO:10 of the instant invention (taught by Brown and Bertelli). The person of ordinary skill in the art would have been motivated to do so because the Klugbauer reference teaches the use of RNA to generate cDNA libraries (page 684, column 2, last paragraph), to identify tissue distribution (page 686, Figure 2) and in situ hybridization methodologies (paged 687, figure 3). One would reasonably have expected success because methods that isolate and identify RNA molecules are well known in the art, and indeed, Klugbauer et al. have shown this methodology to be successful in isolation and identification of RNA encoding molecules which are also members of the $\alpha_2\delta$ subunit family.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shulamith H. Shafer, Ph.D. whose telephone number is 571-272-3332. The examiner can normally be reached on Monday through Friday, 8 AM to 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback, Ph.D. can be reached on 571-272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the latent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Elizabeth C. Kemmerer

ELIZABETH KEMMERER
PRIMARY EXAMINER

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